REMARKS

Claims 13-16 have been canceled and replaced by new claims 17-20, claims 4-12 have been withdrawn from consideration and, therefore, claims 1-3 and 17-20 remain in the application.

The Examiner's rejection of Applicants' claims under 35 U.S.C. §112, 35 U.S.C. §103, and 35 U.S.C. §102 are traversed and reconsideration is respectfully requested. Applicant has amended the specification, has added the inadvertently omitted portions of Table II; and, has rewritten claims 13-16 as new claims 17-20. It is respectfully submitted that these amendments have overcome the Examiner's rejections under 35 U.S.C. §112.

In response to the rejection of claims 1 and 13-16 as obvious in view of the Brattsand et al. patent (U.S. Patent No. 3,983,233), Applicants note that while the compounds claimed in the present application are structurally similar to those described in the Brattsand et al. patent, none of the products claimed in the instant application are specifically included in this Brattsand et al. patent, nor are they included in the patents of MacDonald et al. (U.S. Patent No. 4,835,145) or Diassi et al. (U.S. Patent No. 3,079,384).

The structure of the products claimed correspond to the basic structure of the glucocorticoids with anti-inflammatory activity as taught by Szefler (See Information Disclosure Statement submitted herewith: "General Pharmacology of Glucocorticoids" by Stanley J. Szefler). All of the corticoids act through the same cellular

mechanisms (See Information Disclosure Statement submitted herewith: "Mechanisms of Glucocorticosteroid Action - Bronchial Asthma" by Michael Kaliner, M.D.) stimulating the same receptors (See Information Disclosure Statement: "Molecular Biology of Glucocorticoid Hormone Action" by Margot C. LaPointe et al.). The modifications which are produced maintaining the basic structure are related to quantitative modifications of the same pharmacological responses.

C. S. Ted Tse et al. (See Information Disclosure Statement submitted herewith: "Corticosteroid Aerosols in the Treatment of Asthma" by C. S. Ted Tse et al.) shows the essential groups for the anti-inflammatory activity within the basic glucocorticoid structure. If these groups are maintained, this pharmacological activity is also maintained. For this reason, from a general point of view, all of the compounds structurally related to those presently claimed (and also to those included in the reference patents cited by the Examiner) show qualitatively common pharmacological properties.

In 1976, Brattsand et al. pointed out the clinical need to obtain corticoids with a lower incidence of unfavorable systemic side effects (U.S. Patent No. 3,983,233) and the structures claimed in their patents supposed an approach in this way. From that point, a number of investigations were conducted on corticoids with a structure similar to that of the compounds cited by Brattsand et al. (U.S. Patent No. 3,983,233, and U.S. Patent No. 3,992,534), but produced only limited improvement in the therapeutic treatment of

anti-inflammatory diseases. Among other authors are Brattsand himself with later works and MacDonald.

From a quantitative point of view, both the general pharmacological activity, as well as the relationship between local and systemic effects of this type of compound, depend essentially on the nature of the substituent radicals, and relevant differences could be found between compounds with structurally similar radicals. This relationship is entirely unpredictable and is not obvious. This becomes apparent from the data contained in Table 5 of the Brattsand et al. patent, Tables II and III of the MacDonald et al. patent, and Table III of the present application.

Table 5 *

Table summarizing biological effects of investigated compounds.

Compound according to Ex. No.	Required dose γ/animal to obtain: 50 % inhibition of Granuloma growth	50 % inhibition of Thymus weight	25 % inhibition of Body weight increase
Triamcinolone acetonide	125	70	100
1	35	100	140
2	10	>30	>30
3	<3	70	170
4	17	130	>270
5	<30	>30	>30
Fluocinolone acetonide	50	14	20
6	5	10	50
7	<3	25	30
8	<30	>30	>30
Prednacinolone acetonide	270	105	>270
9	100	80	80
10	10	175	90
11	<30	>270	30
12	<30	>270	270
13	<3	25	20
14	7	35	10
15	15	17	25
16	<3	30	20
17	<7	50	30
20	<3	10	10
21	10	30	20
22	<3	10	5
26	<3	60	40
27	3	90	70
29	<3	60	20

* From U.S. Patent 3,983,233 (col. 9)

TABLE II *

Compound	Relative Topical Anti-Inflammatory Potency (Budesonide = 1)
Ex. 3 USP 4,404,200	0.39
2e	3.03
2f	4.86
2g	1.80

* From U.S. Patent 4,835,145 (col. 3)

TABLE III *

Compound	Relative Topical Anti-Inflammatory Potency (Budesonide = 1)
Ex. 22 USP 3,983,233	1.49

TABLE III-continued *

Compound	Relative Topical Anti-Inflammatory Potency (Budesonide = 1)
2i	5.90

* From U.S. Patent 4,835,145 (cols. 3 and 4)

TABLE III *

LOCAL PHARMACOLOGIC ACTIVITY AND SYSTEMIC GLUCOCORTICOID EFFECTS EXPRESSED AS ED_{50} µg/pellet

COMPOUND	EPIMER	TOPICAL ANTI-INFLAMMATORY ACTIVITY (Cotton Pellet)	SYSTEMIC GLUCOCORTICOID ACTIVITY (Thymus inhibition)	THERAPEUTIC INDEX SYSTEMIC ED_{50}/ TOPICAL ED_{50}	THERAPEUTIC INDEX WITH RESPECT TO BUDESONIDE
7	22 R,S	21.7 (17-27.7)	614.7 (279.6-1351)	28.3	26
8	22 S	20.5 (16.9-25.6)	608 (359.3-1228.3)	29.6	27.2
9	22 R	25.4 (18.2-31.1)	667.1 (321.4-1489.2)	26.2	24.5
10	22 R,S	59.9 (59.3-60.3)	583.2 (236.2-1440)	9.7	8.9
11	22 S	43 (38.4-58)	555.3 (296.3-1387.3)	12.9	11.8
12	22 R	74.7 (85.3-65.1)	592.2 (265.1-1342.9)	7.9	7.2
13	22 R,S	4.5 (3.7-5.5)	54 (35-83.3)	12	11
14	22 S	3.6 (3-4.5)	49 (30.7-76.2)	13.6	15
15	22 R	5.2 (3.6-6)	56.3 (29.8-88.3)	10.8	9.9
BUDESONIDE	22 R,S	163.6 (125.1-213.9)	178.6 (81.3-392.6)	1.09	1
TRIAMCINOLONE ACETONIDE	22 R,S	220.7 (198.1-245.7)	156.4 (144.7-169)	0.7	0.6
FLUNISOLIDE	22 R,S	351.6 (268.8-459.9)	156 (188.3-224.8)	0.44	0.4

* From Patent Application 578,942

From the foregoing, it is clear that a higher intrinsic local activity and a lower systemic glucocorticoid activity are the desirable properties for a new glucocorticoid intended for topical action.

From this perspective, the anti-inflammatory potency of the products of the present invention is compared with the values obtained in the MacDonald et al. patent (Tables II and III) on the bases of their ability to inhibit cotton-pellet induced granulomas (concentration necessary for 50% inhibition, method of Meier (See Information Disclosure Statement submitted herewith: "Zur Frage des Mechanismus der Hemmung des Bindegewebswachstums durch Cortisone" by Meier). The results of relative potency corresponding to our invention are extracted from the ration ED_{50} Budesonide/ED_{50} (22-RS) ("topical anti-inflammatory activity" column of Table III of our application).

The results are shown on the following table:

Relative Topical Anti-Inflammatory Potency

Patent	Compound	Relative Topical Anti-inflammatory Potency (Budesonide = 1)
U.S. Pat. No. 3,983,233 (Brattsand)	Ex. 22 (more potent of all the Brattsand compounds)	1.49*
U.S. Pat. No. 4,835,145 (MacDonald)	2 e 2 f 2 g 2 i	3.03 4.86 1.80 5.90
U.S. Pat. App. No. 578,942	7 10 13	7.54 2.73 36.35

*Table III of U.S. Patent No. 4,835,145

It is clear from these results that the compounds claimed in the present application show a favorable anti-inflammatory potency relative to Budesonide, as compared to the products on the reference patents. This improvement of activity can possible be, in part, attributed to the characteristics of the bulk substituent (See Information Disclosure Statement submitted herewith: "Synthesis and Evaluation of Anti-inflammatory Activities of a Series of Corticosteroid 17 α-Esters Containing a Functional Group" by H. Ueno et al.), and so steric differences in said radical can provide better responses.

MacDonald et al. does not show data regarding the systemic activity of its products.

In the following table, the corresponding therapeutic rates are given in order to compare the balance between the local and systemic activity of the products included in the instant patent application and the compounds particularly preferred in the Brattsand et al. patent, (column 9, line 46, of U.S. Patent No. 3,983,233). In both cases, these rates are given by the ratio DI_{50} inhibition of thymus weight/DE_{50} inhibition of granuloma growth.

Comparison of Therapeutic Indices

Patent	Compound	Therapeutic Index
U.S. Pat. No. 3,983,233	Ex2	23
	Ex3	23
	Ex6	2
	Ex7	8,3
	Ex10	17,5
	Ex14	5
	Ex16	> 10
	Ex20	> 3,3
	Ex22	> 3,3
	Ex26	> 20
	Ex29	> 20
U.S. Pat. App. No. 578,942	7	28.3
	10	9.7
	13	12

From the foregoing values, it is clear that the compounds claimed in the present application show a favorable therapeutic index in relation with the products of the reference patent. This better therapeutic index of the compounds claimed in the present application is due to their better anti-inflammatory local response (Table on Relative Topical Anti-inflammatory Potency of above) and probably to a more rapid metabolization of the compounds of our invention.

Non-desired systemic effects may be observed after the resorption of corticoids. So, for compounds intended for topical use, a fast metabolic or elimination rate is highly desirable and advantageous pharmacokinetic profiles can clearly establish patentability if better characteristics regarding non-desired systemic side effect are achieved. In particular, a rapid and extensive enzymatic inactivation after absorption will be related to minimizing systemic glucocorticoid effect.

In the following table, we summarize several relevant pharmacokinetic and metabolic parameters for compound 7 of the present application and compound of Example 9 on the Budesonide patent (U.S. Patent No. 3,983,233).

Pharmacokinetic Parameters

Parameter	Compound 7	Budesonide
Distribution Volume 1/kg	2.88 - 4.21**	2.5 - 7.7*
Half-life time (hours)	0.9 - 1.12**	1.8 - 3.0*
Plasma clearance (1/h/kg)	0.77 - 0.88II	1.0 - 2.5*
Hepatic metabolism***	86.5%	58%

* Values from (20)
** Data from the study performed by LSR using radiolabeled compound (referred as ^{3}H-EL-876 in that study) (24).
*** Carried out according to the SKF 525 A technique (3).

From the above data and the enclosed bibliography (See Information Disclosure Statement submitted herewith: "Pharmacokinetic Studies of a Potent Glucocorticoid (Budesonide) in Dogs by High-Performance Liquid Chromatography" by A. Ryrfeldt et

al.; "Accion Sistemica De El-876 Y Budesonide Ed Ratas Pretratadas Con SKF 525-A (Inhibicion de la Biotransformacion Hepatica"; and, "EL-876: Absorption and Excretion Study in the Dog") it is derived that, both compound showing similar distribution volume values, half-life time for compound 7 from our invention is 50% lower than Budesonide, in correspondence to a faster hepatic metabolism for compound 7. This metabolic profile support a lower systemic concentration, and so, a lower systemic effect of compound from our invention, as related to Budesonide.

The Examiner specifically mentions compound 16 presented in Table 4, column 5, of Brattsand and col. (A), indicating the structural similarity with the compound claimed by us in which R_1 is butyl and R_2 is acetyl. The present patent application does not cover experimental data on the pharmacological activity of said compound; however, the data are available in our internal files (compound EL-854). The comparison of these data with compound 16 of Brattsand is indicated below:

Topical pharmacologic activity and systemic glucocorticoid effects expressed as ED_{50} μg/pellet

Compound	Topical anti-inflammatory activity (Cotton Pellet)	Systemic glucocorticoid activity (Thymus inhib)	Therapeutic Index Systemic ED 50/ Topical ED50
EX 16 (U.S. Pat. 3,983,233)	< 3	30	> 10
EL-854	8.6	147	17.1

It will, therefore, be clear that although the product of the instant claims has a structure to the broad class of compounds disclosed in the reference, the previously noted therapeutic index clearly rebuts the Examiner's allegations of obviousness.

From comparisons of therapeutic index, it is clear that even though they are structurally related, the compounds claimed in the instant patent applications are not specifically disclosed or suggested by the references, show higher topical anti-inflammatory potency, better relationships between local anti-inflammatory activity (inhibition of the growth of the granuloma) and the systemic effects (reduction of the thymus weight), and more advantageous elimination behavior than the compounds claimed in the reference. This better therapeutic index than the steroids of the prior art is highly unexpected and unobvious.

As a result, the use of the compounds claimed in the present application are not a matter of preference depending on factors not related to pharmaceutical properties, but represents a therapeutic improvement with regard to other steroids and, therefore, are clearly patentable.

In response to the last paragraph of page 6 to page 7 of the Office Action, regarding epimers claimed in our invention, and their structural similarity to the Brattsand et al. compounds (A) and (B), Applicants again disagree with the Examiner and traverse his rejection.

Applicants feel that the differences indicated above between the compounds of claim 1 of the instant application and the reference patents cited by the Examiner are also valid in the case of the isolated epimers of these compounds. While broadly structurally related compounds, the products included in our patent application, as well as those mentioned by Brattsand et al. contain a chiral center in C-22 and consequently they can exist as mixtures of epiments. None of the epimers claimed in the present application are specifically included in or suggested by the Brattsand et al. (U.S. Patent No. 3,992,534).

In the cited Brattsand et al. patent, it is indicated and claimed that compound B has consistently physiologically better characteristics, although this does not mean that component A is less advantageous from a therapeutic point of view (column 10, line 45). This is due to the fact that the greater interest shown with regard to component B corresponds to a higher anti-inflammatory effect and not to a lower systemic effect. Brattsand et al. (U.S. Patent No. 3,992,534) specifically mention the compounds of their Examples 1, 3, 5, 7, 8, and 12 as preferred, based upon the characteristics of component B.

Again, the advantage of the new compounds and epimers claimed in the present application lies in its favorable therapeutic index (high local anti-inflammatory effect with a minimum systemic effect), we consider as other authors do (See Information

Disclosure Statement submitted herewith: "Correlation Between Chemical Structure, Recept Binding, and Biological Activity of Some Novel, Highly Active, 16α, 17 α-Acetal-Substituted Glucocorticoids" by E. Dahlberg et al.; and, "Corticosteroid Aerosols in the Treatment of Asthma" by C. S. Ted Tse et al.), that this must be the criterion for evaluating the utility of the products and their epimers.

The pharmacological data of these compounds and their epimers preferred by Brattsand (Table 3, columns 10 and 11) are compared with the data corresponding to our compounds (Table III of our patent application).

Table summarizing biological effects of investigated compounds and related epimers

Patent	Compound		Γ/animal to obtain 50% inhibition of:		Therapeutic Index ED50 Thymus/ ED50 Granuloma
			Granuloma growth	Thymus weight	
Brattsand (B) U.S. Pat. 3,992,534	Ex 1	A + B	120	270	2.25
		A	270	115	0.42
		B	30	50	1.66
	Ex 3	A + B	10	> 30	3
		A	25	> 30	1.2
		B	3	17	5.6
	Ex 7	A + B	no data	no data	-
		A	15	12	0.8
		B	10	6	0.6
	Ex 8	A + B	5	10	2
		A	6	13	2.1
		B	4	10	2.5
	Ex 12	A + B	100	80	0.8
		A	125	125	1
		B	40	70	1.75
U.S. Pat. App. 578,942	7 22 R,S		21.7	614.7	28.3
	8 22 S		20.5	608	29.6
	9 22 R		25.4	667.1	26.2
	10 22 R,S		59.9	583.2	9.7
	11 22 S		43	555.3	12.9
	12 22 R		74.7	592.2	7.9
	13 22 R,S		4.5	54	12
	14 22 S		3.6	49	13.6
	15 22 R		5.2	56.3	10.8

It is clear from this table that in all the cases, the therapeutic rates of our products and their epimers are

unexpectedly and unpredictably more favorable than those shown by the compounds mentioned by Brattsand et al. and component B of the afore-mentioned Brattsand compounds.

As a result, it is again clear that even though they are broadly structurally related, the epimers claimed in the present application are neither specifically mentioned nor in any way suggested by, and clearly show a better relationship between local anti-inflammatory activity and systemic effects than the epimers claimed in the reference patent. A better therapeutic index than that of the steroids of the prior art is clearly and unexpectedly obtained. This means a significant therapeutic improvement in relation with other glucocorticoids.

While the corticose steroids of the present application are broadly structurally similar to those disclosed in the cited references, they are neither disclosed by any of those references nor obvious from these references particularly in view of the highly unexpected improvement in therapeutic results obtained by employing the corticose steroids of Applicants' invention. In view of this, Applicants respectfully maintain that all of the claims presently in the application are clearly patentable and unobvious

over the references cited by the Examiner. A Notice of Allowance and passage of the case to issue are, therefore, respectfully solicited.

Respectfully submitted,

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CERTIFICATE OF MAILING

I hereby certify that this Amendment is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Hon. Commissioner of Patents and Trademarks, Washington, D.C. 20231, on December 9, 1991.

Sally A. Major